



Timing of major fracture care in polytrauma patients – an update on principles, parameters and strategies for 2020

Pape, H-C ; Halvachizadeh, Sascha ; Leenen, L ; Velmahos, G D ; Buckley, R ; Giannoudis, P V

Abstract: Objectives Sustained changes in resuscitation and transfusion management have been observed since the turn of the millennium, along with an ongoing discussion of surgical management strategies. The aims of this study are threefold: a) to evaluate the objective changes in resuscitation and mass transfusion protocols undertaken in major level I trauma centers; b) to summarize the improvements in diagnostic options for early risk profiling in multiply injured patients and c) to assess the improvements in surgical treatment for acute major fractures in the multiply injured patient. Methods I. A systematic review of the literature (comprehensive search of the MEDLINE, Embase, PubMed, and Cochrane Central Register of Controlled Trials databases) and a concomitant data base (from a single Level I center) analysis were performed. Two authors independently extracted data using a pre-designed form. A pooled analysis was performed to determine the changes in the management of polytraumatized patients after the change of the millennium. II. A data base from a level I trauma center was utilized to test any effects of treatment changes on outcome. Inclusion criteria: adult patients, ISS > 16, admission < less than 24 h post trauma. Exclusion: Oncological diseases, genetic disorders that affect the musculoskeletal system. Parameters evaluated were mortality, ICU stay, ICU complications (Sepsis, Pneumonia, Multiple organ failure). Results I. From the electronic databases, 5141 articles were deemed to be relevant. 169 articles met the inclusion criteria and a manual review of reference lists of key articles identified an additional 22 articles. II. Out of 3668 patients, 2694 (73.4%) were male, the mean ISS was 28.2 (SD 15.1), mean NISS was 37.2 points (SD 17.4 points) and the average length of stay was 17.0 days (SD 18.7 days) with a mean length of ICU stay of 8.2 days (SD 10.5 days), and a mean ventilation time of 5.1 days (SD 8.1 days). Both surgical management and nonsurgical strategies have changed over time. Damage control resuscitation, dynamic analyses of coagulopathy and lactate clearance proved to sharpen the view of the worsening trauma patient and facilitated the prevention of further complications. The subsequent surgical care has become safer and more balanced, avoiding overzealous initial surgeries, while performing early fixation, when patients are physiologically stable or rapidly improving. Severe chest trauma and soft tissue injuries require further evaluation. Conclusions Multiple changes in management (resuscitation, transfusion protocols and balanced surgical care) have taken place. Moreover, improvement in mortality rates and complications associated with several factors were also observed. These findings support the view that the management of polytrauma patients has been substantially improved over the past 3 decades.

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Title

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Level of Evidence: III

Abstract

Objectives: Sustained changes in resuscitation and transfusion management have been observed since the turn of the millennium, along with an ongoing discussion of surgical management strategies. The aims of this study are threefold: a) to evaluate the objective changes in resuscitation and mass transfusion protocols undertaken in major level I trauma centers; b) to summarize the improvements in diagnostic options for early risk profiling in multiply injured patients and c) to assess the improvements in surgical treatment for acute major fractures in the multiply injured patient.

Methods:

I. A systematic review of the literature (comprehensive search of the MEDLINE, Embase, PubMed, and Cochrane Central Register of Controlled Trials databases) and a concomitant data base (from a single Level I center) analysis were performed. Two authors independently extracted data using a pre-designed form. A pooled analysis was performed to determine the changes in the management of polytraumatized patients after the change of the millennium.

II. A data base from a level I trauma center was utilized to test any effects of treatment changes on outcome. Inclusion criteria: adult patients, ISS > 16, admission < less than 24 hours post trauma.

Exclusion: Oncological diseases, genetic disorders that affect the musculoskeletal system.

Parameters evaluated were mortality, ICU stay, ICU complications (Sepsis, Pneumonia, Multiple organ failure).

Results:

I. From the electronic databases, 5,141 articles were deemed to be relevant. 169 articles met the inclusion criteria and a manual review of reference lists of key articles identified an additional 22 articles.

II. Out of 3,668 patients, 2,694 (73.4%) were male, the mean ISS was 28.2 (SD 15.1), mean NISS was 37.2 points (SD 17.4 points) and the average length of stay was 17.0 days (SD 18.7 days) with a mean length of ICU stay of 8.2 days (SD 10.5 days), and a mean ventilation time of 5.1 days (SD 8.1 days).

Both surgical management and nonsurgical strategies have changed over time. Damage control resuscitation, dynamic analyses of coagulopathy and lactate clearance proved to sharpen the view of the worsening trauma patient and facilitated the prevention of further complications. The subsequent surgical care has become safer and more balanced, avoiding overzealous initial surgeries, while performing early fixation, when patients are physiologically stable or rapidly improving. Severe chest trauma and soft tissue injuries require further evaluation.

Conclusions:

Multiple changes in management (resuscitation, transfusion protocols and balanced surgical care) have taken place. Moreover, improvement in mortality rates and complications associated with several factors were also observed. These findings support the view that the management of polytrauma patients has been substantially improved over the past 3 decades.

Level of Evidence: III

Key words: polytrauma, resuscitation, soft tissue injuries, acid base changes, lactate clearance, coagulopathy, damage control.

INTRODUCTION

Over the last two decades complication rates in patients with multiple injuries have decreased (1, 2). The causes may partially lie in the improvement of safety factors, both for motor vehicle passengers (3, 4) and for pedestrians involved in motor vehicle accidents (MVA) (5). Apart from these road safety issues, numerous changes have been made in clinical patient management. There is no doubt that more precise identification of the patient at risk for complications in the early stages after trauma is available (6-9). Also, there is a higher awareness of life-threatening complications (10-13), possibly related to the availability of numerous clinical parameters and biomarkers for the prediction of clinical complications (14 - 17).

The observed improvement in outcome in a critically injured patient with fractures is also striking. Improvements in early diagnostic tools (15-17), surgical techniques and staged management of fracture fixation has been seen to play a role (18-22). In general, surgical treatment strategies have

become more individualized (23), especially in life-threatening injuries to the chest, abdomen and for major fractures (24-28). In a similar fashion, endpoints of transfusion, management of coagulopathy and end points of resuscitation appear to have been better defined (29). Other interdisciplinary trauma care groups suggest that the improvement in outcome is also related to better management of coagulopathy, in addition to those achieved by balanced surgical strategies (9).

Although many of the studies mentioned above suggest changes in various factors (including management of resuscitation, coagulopathy, supplementation of blood products, and safe surgery), there is currently no review that summarizes these. To address this gap in the literature, we performed a systematic review that synthesizes the available evidence to inform clinical practice and to guide future research. The aims of this study are as follows:

1. To describe the changes in resuscitation and mass transfusion protocols in multiple injured patients with severe hemorrhage
2. To summarize the developments of diagnostic tools for early profiling of the multiple injured patient
3. To assess the quality and options of different surgical treatment strategies for acute major fractures in multiple injured patients
4. To compare the development and the outcome of multiple injured patient in literature with the database of one Level 1 trauma center

METHODS

Part 1: Systematic review

Eligibility criteria

This systematic review was conducted based on a prior review protocol registered with the International Register of Systematic Reviews (PROSPERO registration). The protocol and review have been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (30).

We focused on the following eligibility criteria for multiple injured patients: 1) Studies investigating changes in the management in parameters of resuscitation and mass transfusion protocols (treatment of nonsurgical bleeding), 2) Studies providing reliable information assessing diagnostic tools, including scoring systems, to facilitate profiling of multiple injured patients, 3) Studies that provide reliable information assessing fracture management in the multiple injured patient.

Case reports, defined as studies reporting data on a sample size of less than 5 patients were excluded in this study. There was no further restriction of study designs. Results from meeting abstracts were included in a separate analysis and only included when found to be relevant or promising enough to warrant future publication in a peer reviewed journal. This was deemed important to minimize publication bias and test the stability of our review's conclusion. Original articles were included if published between Jan 1, 1999 and May 15, 2019. No language restrictions were applied. Data sources include MEDLINE, Embase, Web of Science, and Cochrane Register of Controlled Trial database (CENTRAL), regional databases and references of included studies. Trials that reported about multiple injured patients and their incidence of complications were included. Disagreements were resolved in discussion.

Screening and Assessment of Eligibility

Two independent reviewers (HCP and PG), both with methodological expertise and with content expertise independently reviewed the titles and abstracts of articles identified in the literature searches in order to determine if the articles should be considered for inclusion. The reviewers erred on the side of inclusivity and any disagreements resulted in the article proceeding to full-text review. Subsequently, both authors independently reviewed the full-text articles that were identified in the title and abstract screening for final inclusion. Any conflicts were discussed in order to achieve consensus. Articles that met the inclusion criteria were selected for data extraction. The other reviewers (LL, SH, RB, and GV), all with methodological expertise and with content expertise performed an assessment for feasibility and plausibility and the content regarding the conclusions made.

Methodological Quality

Authors independently graded the methodological quality of each included study. Observational studies were evaluated using the Methodological Index for Non-Randomized Studies (MINORS) (31). Randomized controlled trials (RCTs) were assessed with the Cochrane Collaboration's Risk of Bias Tool (32). This review includes the following MeSH terms: Abbreviated Injury Scale, accidental Falls/statistics & numerical data, accidents, Traffic/statistics & numerical data, angiography/methods, algorithms, arteriovenous Fistula/etiology, Adult, Biomarkers/blood, arterial injury, Brain Injuries, Traumatic/blood, Brain Injuries, coagulopathy, clinical Coding/methods, consensus, Extravasation of Diagnostic and Therapeutic Materials/etiology, Female, Hemoperitoneum / etiology Humans, Injury Severity Score, Glasgow Coma Scale Traumatic/mortality, Injury Severity Score, / epidemiology, incidence, multiple trauma/diagnosis, Lactic Acid/blood, Lactic Acid/pharmacokinetics, Multiple Trauma/epidemiology, observer variation, prospective studies, registries, trauma centers/statistics &

numerical data, United States/epidemiology, Europe /epidemiology, Injury Severity Score, major fractures, Male, Patient Admission, Patient Selection, Retrospective Studies, Salvage Therapy, Spleen/injuries, Tomography, X-Ray Computed, Trauma Centers, Treatment Outcome, Violence/statistics & numerical data, Wounds, Nonpenetrating/complications, Wounds, Nonpenetrating/diagnosis, Wounds, Nonpenetrating/epidemiology, Predictive Value of Tests, Wounds, Nonpenetrating/therapy.

The following particular subheadings were selected by the reviewers: emergency room management and resuscitation strategies; Diagnostics and management of coagulopathy; Diagnostics of acid-base changes; Scoring and management of orthopedic injuries; Soft tissue injuries (e.g. chest trauma and thoracic trauma, reperfusion).

Part 2: Database analysis

The database includes multiply injured patients treated at one Level 1 trauma center, as pointed out in detail in previous publications (142,144).

Briefly, the database analysis was utilized as follows:

Inclusion / Exclusion criteria

The study population had to fulfil the following inclusion criteria: adult patients, treated due to polytrauma (ISS > 16 points) at one Level 1 trauma center, and an admission time of less than 24 hours after injury. Patients with oncological diseases, chronic diseases, and genetic disorders that affect the musculoskeletal system were excluded.

Data management

During the development of the data base, all injuries are classified by the trauma physician who also routinely performs scoring of injury severity. Approval by the local institutional review board (IRB) according to IRC guidelines (No. St. V. 01-2008) was obtained. Data include twice daily entries of clinical and physiological parameters and organ function scores during the first three weeks of admission. It contains data for clinical chemistry, hemostasis, and parameters associated with artificial ventilation. Admission data were documented for the emergency room, all further laboratory data were acquired on daily basis, if needed, several times per day. All complications were documented

during the clinical course, including ICU scores, pneumonia, sepsis and adult respiratory distress syndrome.

Definitions

In hospital mortality described was diagnosed when a patient succumbed during the first hospital stay.

The *intensive care stay* (ICU-stay) summarized the time (days) between admission and discharge from the intensive care unit (ICU). The intermediate care stay (IMC-stay) was defined as between admission and discharge from the IMC.

Pneumonia was diagnosed according to the diagnoses in the manuscripts. Most of them used the following criteria; body temperature - at least 38.5°C and one of the following criteria; infiltrate on chest x-ray in the absence of ARDS or positive culture in bronchoalveolar lavage fluid.

Multiple organ failure (MOF) was diagnosed according to a scoring system, when available in the references.

For the purpose of the current study, a comparison was made for outcome-based parameters and the general mortality rate, the rate of 72-hour mortalities, and complications which were separately investigated.

Complications during the hospital stay were defined as those occurring during the stay of intensive care, such as Pneumonia, Multiple organ failure and Sepsis.

Group distribution

It was thought to account for the changes in surgical management for major fractures, and nonsurgical changes, such as volume management and transfusion guidelines.

In the current level I center, limitations of the amount of initial surgery (damage control techniques(33)) were not routinely performed before 2002. Damage control techniques were routinely performed thereafter. Later, a change in transfusion guidelines was developed after 2007.

Three different time periods were separated as follows:

Group no DC

(< 2002; no limitations in duration of surgery at day I)

Group DC

(2003 – 2007; application of damage control techniques for major fractures in unstable patients)

Group DC Tr

(> 2007; application of new transfusion guidelines in addition to staged surgical management)

Therefore, the three groups are thought to represent either changes in the surgical management (group no DC versus DC) and surgical versus nonsurgical management changes (group DC versus DC Tr), (9, 34).

Statistics

Nominally scaled and categorical variables were compared with Pearson Chi-square test, continuous variables with students t-test. Continuous variables are displayed as a mean with standard deviation (SD), categorical variables as numbers (n) and percentages (%). Fitted generalized linear models were used for predictive estimate of scoring systems. Odds ratios (OR) for prognosis of the different endpoints were calculated, along with 95% confidence intervals (CI). Tests were corrected for multiple testing if necessary. Proportions were evaluated using the Yates-corrected statistics. The relative risks of complications were calculated individually and expressed in OR. The associations between conventional parameters and death were evaluated using univariate analysis. Continuous variables are summarized as mean and standard deviation. Statistical significance was assumed at an alpha = 0.05. All calculations were performed using R Core Team (2018) (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: <https://www.R-project.org/>).

RESULTS

Part 1: Systematic review

The electronic database search identified 5141 articles that were deemed to be relevant to the topics listed above. Following review of titles, abstracts, and independent assessment of potential studies, we identified 169 articles that met the inclusion criteria. The manual review of reference lists of key articles identified an additional 22 articles, the manual search of annual meeting abstracts identified 5 eligible abstracts (published in the abstract books of the Orthopaedic Trauma Association (OTA), European Society for Trauma and Emergency Surgery (ESTES), and European Federation of National Associations of Orthopaedics and Traumatology (EFORT), and American Academy of Orthopaedic Surgeons (AAOS)).

All included studies were published or presented after 2000. The majority of studies were single-center initiatives that were conducted in Europe or North America.

Resuscitation strategies

Resuscitation strategies have changed towards permissive hypovolemia. This change had an impact on the general patient outcome (9, 35, 36). The most important new information was gathered by reducing the amount of volume administered, “damage control resuscitation” (29, 37-39). Moreover, a multi-center study (Pragmatic Randomized Optimal Platelet and Plasma Ratios, PROPPR) trial developed the massive transfusion strategy targeting a balanced delivery of plasma-platelet-red blood cell (RBC) in a ratio of 1:1:1 (40). It appears to result in improved survival at 3 hrs. post admission and a reduction in mortality caused by exsanguination in the first 24 hours compared with a 1:1:2 ratio (41). Multiple other study principles were concluded from those results (42, 43), (**Table I**).

Diagnostic tools for early profiling of the multiple injured patient

Coagulopathy

Among the studies indicative of posttraumatic coagulopathy, fifteen were relevant for trauma patients. Among these, five represent guidelines, multicenter studies or systematic reviews. They include dynamic platelet function tests, such as Rotational Thromboelastometry (ROTEM), and other conventional coagulation tests (44-48). In addition ten other studies specifically analyzed dynamic platelet function in terms of their prediction of mortality (49-51), prediction of transfusion requirements and mass transfusions (52-56) (**Table II**).

Diagnostics of acid-base changes

Between 2003 (57) and 2019, multiple studies have been performed assessing acid-base changes (58-62). The majority of these studies indicate an admission lactate level between 2.0 and 2.5mmol/l as a threshold. Two groups selected higher levels 3.0 mmol/l (63) and 4.0 mmol/l (64). The most recent study is a systematic review and the main results are shown in **Table III** (65). It becomes evident, that only one lactate measure is not reliable as a marker for defining the status of a patient (13), but more the clearance capacity of lactate (62, 66-69), (**Table III**).

Scoring systems to determine the timing of surgery

Six different recommendations have been available in the literature (all published later than 2005). Among them, four were deemed to be relevant and are depicted in **Table IV**.

Indications for surgery and their dependency on the severity of injury

Most of the studies that present with recommendations for surgical fixation of major fractures derive from single center analysis (**Table V**). Two publications were done on the basis of a trauma registry, one compares different indications in two centers and one study is an RCT in ten centers. **Table VI**

summarized studies that use lactate and acid base changes as the main indicator for surgical decision making. There is a certain variability in the recommendations regarding the time and the threshold level of lactate. **Table VII** indicates factors that were described in the early stages of the development of staged surgical concepts, thus respecting injury severity and injury distributions. It provides an update on the parameters used today (e.g. replacement of a Swan Ganz catheter etc.) and an update on chest trauma scoring.

Part 2: Database analysis

Demographics

The database analysis includes 3668 patients. Most of the patients were male (n=2694, 73.4%). The mean ISS was 28.2 points (SD 15.1), mean NISS 37.2 points (SD 17.4). The average length of stay was 17.0 days (SD 18.7 days) with a mean length of ICU stay of 8.2 days (SD 10.5 days), and a mean ventilation time of 5.1 days (SD 8.1 days).

Demographic data are displayed in **Table VI**. Stratification was made into three different time periods, 867 patients (23.6%) of which were treated prior to 2002 (before introduction of damage control techniques (Group No DC)). Out of the remaining 2801 patients, 1262 (45.1%) patients belonged to the years 2003 and later (incorporation of damage control techniques for major fractures (Group DC)), and 1539 (54.9%) were treated after 2009 (changes in nonsurgical management, eg. transfusion and fluid management guidelines (Group DC Tr)).

Outcome Parameters

Patients were significantly older in Gr. DC Tr ($43.2y \pm 18.97y$ versus $49.6y \pm 21.35y$, $p < 0.0001$) as a sign of increasing life expectancy. The mortality rate was significantly lower in group DC Tr (19.7%) when compared with group DC (32.7%, $p < 0.0001$). Ventilation time decreased significantly (from $6.4days \pm 8.6days$ to $3.61days \pm 7.0days$, $p < 0.001$). Correspondingly the total ICU-stay decreased (9.4 ± 10.8 to $6.3days \pm 9.1days$, $p < 0.001$). Further results regarding complications are graphically displayed in **Figure 1**.

DISCUSSION

Trauma continues to represent a major cause of severe illness in the working age population (70-72). In many societies, attempts have been undertaken to improve trauma care by implementation of trauma system availability (72, 73), certification strategies for hospital (74) and teaching tools (75).

Among the important physiological principles are the relevance of hypothermia, acidosis and coagulopathy in the trauma patient on admission (76).

Principles of physiologic factors

Multiple parameters are relevant in the management for the physiological changes after multiple injuries and they affect multiple disciplines including general surgeons, anesthesiologists, intensivists and orthopedic surgeons (77, 78).

It has also been confirmed that additional cofactors are crucial in determining the risk of complications. Included in these are severe prolonged hypotension, reperfusion injury and severe chest trauma (79, 80). Inflammatory mediators, such as interleukins have been used for monitoring patients pre-operatively and during the hospital stay (16, 81-84). This is in line with other results from the “*Inflammation and the host response to injury collaborative research program*”, which reinforces the relevance of numerous clinical inflammatory parameters and biomarkers for the prediction of clinical complications (14). However, their inclusion as a decision-making factor has been limited to certain trauma systems and is technically feasible in Level 1 trauma centers only (85). In this line, many centers that admit severely injured patients would not be able to differentiate between different phenotypes within the entirety of global clotting factor abnormalities (86).

Among other factors, the common language in treating these patients is important, and the definition of polytrauma is among them. Between 2006 and 2012, a consensus process took place, guided by members of multiple trauma societies, such as the European Society of Trauma and Emergency Surgery (ESTES), the American Association for the Surgery of Trauma (AAST), the Orthopaedic Trauma Association (OTA), and the German Trauma Society (DGU). Based on multiple discussions and a consensus process, the evidence based criteria to identify patients with increased mortality rates were found to be multifactorial: additionally to AIS the relevance of age, hypotension on admission, GCS on admission, and coagulopathy were identified as relevant risk factors for lethal outcome (87).

Principles of resuscitation

Since the 1980s, the credo of resuscitation was to provide *rapid and aggressive fluid replacement* to avoid any hypoperfusion and, if present, to restore perfusion as rapidly as possible (88). The concept

was believed to be valid throughout the world and was applied both in civilian and military trauma management (89, 90). Thus, resuscitation with crystalloids and packed red blood cells (pRBCs) represented the standard treatment at the beginning of the millennium.

Later, *aggressive volume replacement* was discussed to be the *cause for increased bleeding* in acute life threatening conditions and reopening blood vessels was discussed to occur in association with it. Other disadvantages appeared to be mechanistic, such as an increase of hydrostatic pressure (91-93), decrease in body temperature induced by the volume influx, and subsequent dilutional coagulopathy (94, 95). Further adverse outcomes include increased rates of postoperative ileus, ARDS, abdominal compartment syndrome (ACS), cardiac decompensation, and infectious complications including surgical site and blood stream infections (96).

According to the current understanding, blood loss is increased with increased mean arterial pressure and dilution of clotting factors (97). Therefore, *permissive hypovolemia*, and *damage control resuscitation (DCR)* represent the reference treatment today (95, 98, 99). Among other factors, the reduction in dilutional effects by permissive hypovolemia is thought to enhance and improve clot formation (100).

Although multiple preclinical scoring systems have been described, the availability of systems for the early clinical stages have been sparse. Most of these have focused on the prediction of massive transfusion (101), or used parameters of hemorrhagic shock to describe the risk of complications (102). In contrast, Kutcher et al. recently suggested looking at coagulopathy in a more detailed fashion, as coagulopathic patients present with mixed risk factors, and coagulopathy has deleterious effects independent of injury severity, shock, and the vicious triad (103).

Management of coagulopathy

Up to 35% of patients with severe injuries present with a trauma-induced coagulopathy on admission (47). Abnormal coagulation tests are associated with higher mortality even in the moderately injured, suggesting that their importance may be underappreciated (104). In general, certain principles appear to be relevant in managing coagulopathy:

1. The efficacy of plasma repletion appears to play out in the first few hours of resuscitation
2. Blood volume deficit may be a more sensitive marker of efficacy in some populations
3. Early plasma replacement appears to prevent some patients from going on to require massive transfusion (105)

Platelet count on admission is a commonly used parameter, although it has not been proven useful to guide resuscitation. One of the few studies that deal with the course of the platelet count was published by Stansbury et al., where admission platelet count in critically injured patients was noticed to be normal in most cases and decreases within 24 hours. Low platelet counts at admission and over a further period of days were strongly associated with increased mortality (106). Other authors compared measurement of Factor V, protein C activity, and anti-thrombin III on-scene to in hospital levels. It was found that patients showed parameters to be 60% of normal on hospital admission and trending towards a worsening degree of coagulopathy compared to on-scene, until specific therapy was initiated (107).

The standard parameters to diagnose coagulopathy around the change of the millennium appeared to be INR and platelet count (108). These measures have been incorporated into existing guidelines, despite an obvious lack of evidence (109, 110). It is known that many standard coagulation tests require long turnaround times, i.e. for separation of plasma from red cells that provide information solely of the initial phases of clot formation (111). Further, these tests were developed for congenital bleeding disorders, and their precise role in guiding transfusion therapy in trauma has not been validated (112). Therefore, in addition to platelet counts, multiple dynamic test systems have been developed to rapidly identify these patients including the critical administration threshold (CAT), the assessment of blood consumption (ABC) score, and other dynamic platelet function tests (*diamond of death*) as identified by thrombelastography (TEG). These tests have been recommended in various studies (7, 113-118), while other studies found no evidence for benefit using TEG and ROTEM (119).

Although they were discussed to be user dependent, this category appears to improve, as new devices become available. Likewise, it was recently emphasized that multiple injured patients present with a spectrum of post injury fibrinolysis, possibly identifiable by both rTEG and ROTEM. Citrated rTEG is a quick and effective method to guide hemostatic resuscitation in trauma patients and does not perform inferiorly to the citrated native of citrated kaolin TEG despite the addition of activation factors (52, 120). TEG and ROTEM provide some agreement in their ability to derive fibrinolysis phenotypes to stratify patients into different risk groups. Of note, this information is in view of inclusion of different other variables such as INR, PTT, platelet count, fibrinogen, D-Dimer, etc. (121).

Published Guidelines

Several guidelines for coagulopathy have been published since 2005 (122). Among them is a European guideline, which is renewed on a regular basis (109, 123, 124). Medication for hemorrhage appears to

increase Plasma-Platelet-RBC ratios, which were shown to be associated with improved outcome in 466 massively transfused civilian trauma patients (125). It was therefore debated whether the 1:1 ratio of Fresh Frozen Plasma may be indicated in life threatening post injury coagulopathy (126). Some suggest that the critical threshold for survival in civilian patients sustaining post injury life threatening coagulopathy may be in the range of 1:2-3 FFP:pRBCs, as the lowest predictive probability of mortality of 0.2 to 0.3 is the case. Albeit, the use of massive amounts of FFP, ARDS rates are not affected (127).

The common definition of *massive transfusion* (10 units RBCs per 24 hours) has been *changed to 10 units RBCs per 6 hours* to better reflect the dominant time period of the acute hemorrhagic event, as well as the associated physiologic consequences. Meanwhile, *goal directed therapy* represents the current standard (128, 129). Along with these changes, the use of additional medication such as Tranexamic acid (TXA) have been shown to be important in acute hemorrhage conditions; some suggest an enhancement of clot formation (130), a group of patients presenting with depletion of fibrinolysis treated with TXA to develop a significantly improved fibrin clot strength (117, 131-135).

Importance of Acid Base changes

There is a long and significant history regarding patient assessment using acid base changes (136, 137). Likewise, the development of the calculation of lactate clearance dated back to the early 1960s, where an improved lactate value was calculated as percentage change of initial lactate value and secondary lactate value: $\frac{(IL-DL)}{IL} \times 100\%$ (136). Since then, various authors have looked at issues of resuscitation based upon changes in pH, lactate and base excess (BE) (138-140). In 2012, a time correction was added and the percentage clearance per hour was described (143). Four categories were developed based upon lactate level and the threshold of 2.5mmol/l: IL and DL \leq 2.5; IL > 2.5 and DL \leq 2.5; IL \leq 2.5 and DL > 2.5; IL + DL > 2.5 and appear to be indicative of early hemorrhage induced mortality (144).

Acid-Base changes appear to play an important role in the management of resuscitation and prediction of complications. It has been applied for prehospital assessment of trauma patients, usually to predict complications and mortality (141). Admission lactate has been used to predict sepsis, especially in the presence of substantial initial hemorrhage (142).

To our knowledge, the first publication to use the term “lactate clearance” looked at lactate measures at 8, 16, 24, 36, and 48 hours after injury; the threshold level was set at 2mmol/l, comparable to other authors (**Table III**). They concluded a survival rate of 75% after normalization of lactate levels between 24 and 48 hours (145). Nevertheless, the differentiation of arterial and venous blood gas analysis (BGA) remains important. This was believed to be rather reliable for many years (146), until a recent

systematic review described hyperlactemia with rather poor agreement between arterial and venous BGA. The authors further concluded that a threshold level of 2.0 mmol/l for screening and arterial BGA for confirms hyperlactemia (147). Several authors defined differing threshold levels depending on their research question (**Table III**), the most commonly used threshold level being between 2.0 and 2.5 mmol/l (143).

Dezman et al. investigated the relevance of elevated lactate levels in trauma patients upon admission. They summarized patients treated between 2010 and 2012 with an admission lactate level of >3mmol/l. Patients were included who had two lactate measures within 24 hours: Group 1 normalized lactate within 24 hours (high clearance), and Group 2 without improvement of lactate level within 24 hours (poor clearance). Based on this methodology, they concluded a superiority of 24 hour lactate clearance compared to initial lactate value (63, 148). Each group included about 25% penetrating injuries. In Group 1 (high clearance), the initial blood pressure and the associated heart rate were substantially better compared to Group 2 (poor clearance). Therefore, it is important to consider their exclusion criteria: patients without lactate measurements within 24 hours, patients that were transferred to the trauma center, or those who died within 15 minutes of arrival. In the vast majority of included patients, the lactate level was not elevated.

Failed lactate clearance is associated with increased mortality. The majority of authors set a threshold level of *lactate between 2.0 and 2.5 mmol/l*. Higher threshold levels were only used by two authors (**Table III**) (63, 149). Further, it is unclear whether arterial or venous levels should be utilized. A clear difference between both approaches has not yet been proven. In the interpretation of lactate level, certain preexisting conditions have to be considered: alcohol consumption (150), chronic renal failure, metabolic diseases (151), medication, sepsis, seizures, CO-poisoning, strenuous exercise, and respiratory or hepatic failure all influence baseline lactate levels and lactate clearance (152, 153). Therefore, we feel that sole use of lactate value to guide management in polytrauma patients may be dangerous and is not advisable.

Early prediction of complications

Prediction of outcomes after injury is traditionally based upon injury severity and stratification thereof. To improve the mere anatomic-based outcome model, physiologic changes and measures for shock were added (87). A single center study described a prediction model for mortality with the main weight on GCS (22%), followed by BE (8%), requirement of blood transfusion (8%), ISS (5%), and age (4%). This model had a 63% sensitivity, and a 94% specificity (ROC 0.96) (154). Our group developed an easy to use and reliable score to allow stratification of multiple injured patients and allow safe

definitive fixation in stable patients (155). The ONPOINT study group investigated an automated analysis of pulse oximetry signals and laboratory values. They used automated analysis of triage vital signs during 15 minutes of pulse oximetry signals. Laboratory values predicted the use of blood transfusion during trauma resuscitation (156). The authors discussed automated calculations from a noninvasive vital sign monitor interfaced with a point-of-care laboratory device to support clinical decisions by recognizing patients in need of transfusion. These features improve prediction of early mortality compared to heart rate and systolic blood pressure (shock index) alone (157).

Ultrasound was discussed as equally useful as laboratory testing as a measure of volume responsiveness in trauma patients by monitoring the vena cava and adjacent structures (158). In a clinically relevant heterogeneous population, ultrasound was only moderately predictive of volume resuscitation requirements whereas the change in diameter of the inferior vena cava was not found to be predictive.

Based on a survey in 2013, the 48 - hour ventilation period has been found to be predictive for complications (159). Patients that developed complications had a lower initial GCS and lower ISS. Further, lung contusion and ventilation duration more than 48 hours were associated with development of further complications (159).

Scoring of the trauma patient for the management of orthopaedic injuries

Over the last two decades, six different scoring systems have been published that attempt to deal with treatment strategies for multiple injured patients (64, 80, 101, 155, 159, 160). Both scoring methods published by Dienstknecht (159) and Ogura (101) require extended observation times (48 hours) for completion and were not deemed to be feasible for clinical use in the acute phase.

The remaining four scoring systems show considerable differences that appear to depend upon the initial research question that led to the development of the given score. The overall goal was to stratify injured patients to give treatment recommendations, but the methodology and the included variables differ substantially (**Table IV**). The initial grading system was published in 2005 and it summarized numerous parameters published by various authors. Subsequently, modifications were made based on the availability of the local data base. The modifications included the omission of Factor II and V, fibrinogen, D-Dimer levels, the Advanced Trauma Life Support (ATLS) classification for shock, urinary output, the $\text{PaO}_2/\text{FiO}_2$ ratio, and the Thoracic Trauma Score (160). Furthermore, patients without chest trauma were included, the threshold values of lactate were changed and the frequency of pRBCs administered were lowered. The resulting scale was named mCGS (modified clinical grading scale), as

the authors used the term Clinical Grading Scale, as the parameters published in 2005 lacked a name. These modifications resulted in a poorer predictive capability of the mCGS compared to the scale published in 2005. The modifications induce a selection bias towards a population that has a different risk profile for systemic complications and is therefore not comparable with the original recommendation (161).

The development of the early appropriate care (EAC) protocol aimed to identify patients cleared for definitive surgery. It uses admission lactate with a threshold level of 4 mmol/L, below which patients are thought to be cleared for any major surgery.

The Polytrauma Grading Score (PTGS) was developed based on clinical and laboratory parameters on patient admission. Patients were later stratified according to mortality rate. The stratification leads to either stable, borderline, unstable or in extremis patients. The management strategies are based upon the strata of the multiple injured patient.

Recommendation guidelines for orthopedic injuries in polytrauma

The controversies in the literature regarding timing of definitive fracture fixation for polytrauma patients is ongoing. Much has been learned from those authors that appear to perform early definitive stabilization in almost any patient versus those that have been accused of delaying definitive fracture care. Options regarding geographic, or trauma system related differences were displayed in a matched paired analysis including patients treated in the United States and patients treated in Europe and revealed comparable timing of fracture fixation despite different trauma systems (162).

As indicated in **Table V**, most authors appear to respect the injury severity of a given population of polytrauma patients and split their recommendations towards either early definitive or early temporary fracture fixation. Because of this, patients with higher ISS are less likely to be treated with early definitive fracture fixation. This trend is independent of the general conclusion of the given publication, and independent of the general use of damage control strategies (163). Moreover, authors that favor early definitive stabilization in all patients have a considerable number of patients with nonoperative management of the major fracture (164), or place patients with initial external fixation into the late fixation group (64), affecting the results and the conclusions.

Historical Background of published recommendations (table VIII)

Early Total Care (ETC)

This concept was coined by various authors and was made popular by many authors, given the fact that the rule used to be not to treat major fractures due to the fear of fat embolism. Bone and Johnson published the first randomized controlled study on this subject and proved that early fixation of isolated fractures and a group of multiply injured patients was beneficial (165). They performed definitive fixation of major extremity fractures within 24 hours after patient admission. The simplified focus of the study attributed fractures of long bones to ARDS and the aim was to reduce pulmonary complications, as ARDS represented the most important complication. Patients included in their study were less severely injured compared to patients in subsequent studies. They included 95 isolated femur fractures and 83 multiple injured patients, less than half of which (40 patients) had indication for ventilation. Further, the authors used the Hospital Trauma Index to calculate the ISS, which also provides higher values compared to the AIS (166, 167).

Damage Control Orthopaedics (DCO)

This concept was first described by Scalea in 2000 (168), and appeared to be relevant, as an increasing number of patients were recognized to leave operating rooms in compromised conditions after prolonged early surgeries (169). Additionally, certain aspects of initial injury types were observed to imply a special risk for secondary complications including SIRS, MOF, sepsis, or ARDS. With DCO treatment, the survival and the rate of complications was improved (170-175). This observation was supported by a prospective randomized study that showed a reduction of acute lung injuries in borderline patients (12), two supportive trauma registry analyses from the NTDB and Tr_DGU, and a matched pair analysis (162). As a result damage control orthopedics appears to represent a feasible option for patients at special risk and has been applied worldwide, independent of trauma center, geographic or treatment differences (174, 176-181).

Early Appropriate Care (EAC)

More recently, emphasis was placed on elevated lactate levels with the similar background, i.e. to all stabilize fractures definitively, whenever lactate stabilizes. It was developed in a retrospective data base and suggests performing definitive stabilization of all major fractures, when lactate levels decrease. It is thus similar to ETC (64).

Safe Definitive Surgery (SDS)

This concept was developed to refine DCO strategies and avoid overzealous use of external fixation “for convenience”. Thus, it attempted to describe steps to separate patients at special risk to develop complications over time (182). SDS uses easily available routine clinical parameters and reflects upon the overall injury severity and distribution of injuries as a basis to understand the dynamic clinical changes that may ensue within hours after injury. It includes criteria for completion of resuscitation at the end of the trauma bay period (183). The continual reassessment of patients at risk is a crucial factor and is suggested to be performed multiple times, i.e. after completion of resuscitation, after completion of a major surgical step in planned staged management of fractures and prior to surgery in the ICU (161).

Prompt Individualized Safe Management (PRISM)

This is a concept that encompasses injury mechanism and distribution, ATLS protocols, physiological state, early diagnostics, and the patient response. The individualized approach includes patient age, gender, co-morbidities and special aspects that may cause management changes, such as pregnancy. In addition to the previous recommendations, it reflects upon local resources both in terms of manpower and hospital capacity. Moreover, this tactic overcomes previous dogma, (such as the “window of opportunity” for certain major fracture fixations) by not recommending setting time limits for initiation of surgery. It therefore respects recent advances in patient assessment using inflammatory mediators and allows one to perform intra-operative reassessments. The authors describe it as representing a philosophy of “doing no further harm” in patients with multiple injuries in order to achieve the best possible outcome in a given patient, hospital, and trauma system environment (184). It may be supported by the fact that complication rates are similar despite treatment in different trauma centers, when staged surgical management of major fractures is performed (162).

Certain criteria about the published treatment guidelines and protocols are summarized in table VIII.

Current risk factor assessment and integration into the results from a level I trauma center

In the current literature, multiple new factors have been summarized and they appear to consist of factors caused by the initial trauma (static), which can then be modified rapidly (dynamic) by rescue conditions, treatment strategies (management of resuscitation, massive transfusion, surgical strategies and perioperative care).

As far as blunt chest trauma is concerned, the most recent literature forecasts the following:

The availability of scoring systems regarding chest trauma has improved the prediction of complications and may be worth considering (185). Specifically, the thoracic trauma score has been shown to be equal or even superior to other scoring systems. It might serve as a predictor of pulmonary failure and also is more precise compared to the AIS thoracic alone (186-188).

Although it has been speculated that the incidence of ARDS has declined and its importance in the survival after trauma has declined, this effect has not been confirmed in recent trauma studies. A systematic review and meta-analysis showed no trend in the incidence of trauma-induced ARDS across the last three decades. There was no significant geographical difference in the incidence of posttraumatic ARDS (comparing United States 13.4% and Europe 12.5%) (79).

It has been argued that the importance of pulmonary failure has declined substantially and acute lung injury (ALI) as a separate entity should be erased; still it continues to be assessed in the literature (189, 190). Certain risk factors were found to be predictive as follows - while blood and plasma transfusion were not independently associated with ARDS, platelet transfusion was a significant independent risk factor. The role of platelets may be explained mechanistically by lung injury models of pulmonary platelet sequestration with peripheral thrombocytopenia. This warrants further investigation (191, 192).

The patient at risk (borderline condition) can be refined as follows - prior to the presentation of the damage control concept, general surgeons implemented the concept of limiting the amount and the duration of the initial operation in a bleeding trauma patient suffering from the triad of death (76, 168, 193). The identification of the patient at risk implies multiple parameters including an ISS > 40 points, multiple injuries in association with thoracic trauma (AIS thoracic > 2), multiple injuries with severe abdominal or pelvic injury, hemorrhagic shock, bilateral major long bone fractures, additional head injury (AIS head > 3) (194). Some of these criteria continue to be of value, and new recommendations are summarized in **Table IX** (195). The timing of operations is recognized as a risk factor for complications and overzealous surgeries are described to be potentially detrimental in patients at risk (196). Likewise, it is confirmed that delayed fracture fixation in the more stable patients is disadvantageous and associated with an increased rate of pulmonary complications (12).

In this line, it is interesting to differentiate between those polytrauma patients that 1) receive treatment within 72 hours that develop complications and major hemorrhage after admission with eventual death and 2) those that develop late complications and mortality. In this line, lactate appears to be a predictor of early death while multiple other parameters appear to predict late death. Our data base analysis has tried to incorporate both, early and late mortality rates. The results obtained in an analysis of 3668 polytrauma patients reveals that the changes in surgical

management was associated with improvements in mortality rates and outcomes (comparison between the outcomes before 2002 (Group No DC) versus 2003-2008 (Group DC), (**Figure 1**). It appears to be relevant for both early and late complications. Subsequently, implementation of protocols of massive transfusion and volume treatment was associated with further improvements in all factors, early and late mortality rates and even for late complication rates (Group DC) versus patient treated after changes in the transfusion and resuscitation management (2009 and later, Group DC Tr), (**Figure 1**). The same was found in a subgroup analysis published by Stein et al. (9). The authors compared two time periods before and after implementation of transfusion guidelines. Their changes were summarized as follows: In 2005–2007, the observed and trauma associated severe hemorrhage score that predicted the incidence of massive transfusion were identical. Whereas in 2012–2014, the observed incidence was less than half that predicted (3.7% vs. 7.5%) and was also proven for red blood cells and fresh frozen plasma.

We are aware of certain limitations apply, as the inclusion of patients with other than orthopedic injuries may have had an effect (inclusion of head trauma patients may interfere with some of the results obtained). Also, one may argue that the treatment of patients before the introduction of balanced surgical tactics may have been critical. However, we aimed at performing a survey on patients treated at time frames of other published data bases, dealing with the same topic (64).

We therefore feel that our data are relevant and supportive of the literature review performed. Interestingly, the striking improvements in outcomes in both time periods occurred in the absence of any other sustained management changes, such as the trauma system, rescue times, patient age, or incidences of chest trauma.

CONCLUSION

In response to the questions addressed in the introduction, we draw the following conclusions:

Resuscitation has changed towards permissive hypovolemia tactics in selected patients. Massive transfusion protocols have been developed and lead to improvement in survival rates. Several management protocols have been developed for the management of major fractures. Validation of any of these protocols is not available to date and should be performed. A patient tailored treatment – individualized medicine approach - is desirable and should cover several pathogenetic pathways to avoid errors described in the current manuscript. Among the existing ones, the PRISM approach appears to be most comprehensive, as it covers issues of rescue, trauma system environment, logistics, and multiple patient factors including patient outcome.

A staged surgical approach has replaced the approach of trying to stabilize all fractures within 24 hours after injury. Obviously, damage control should be limited to those patients at risk, not as an excuse to delay definitive fixation in stable patients “for convenience”. In stable patients, fractures are stabilized as early as possible, based on individual patient physiology rather than a “window of opportunity”. Validation of trauma protocols is required, or development of new ones in the future.

In summary, various innovations have occurred since the turn of the millennium and they have helped evaluate the trauma patient with multiple injuries. Among these, we have identified four major areas: 1) Emergency room management has moved towards a strategy of permissive hypovolemia and point of care testing; 2) The continual reassessment of the trauma patient after resuscitation has become more standardized and involves endpoints of coagulopathy and acid base changes; 3) The criteria to assess borderline patients and those at special risk have been refined; 4) Scoring systems and scales have been described that may help guide the management of patients that may benefit from damage control versus for safe definitive early surgery for major fractures.

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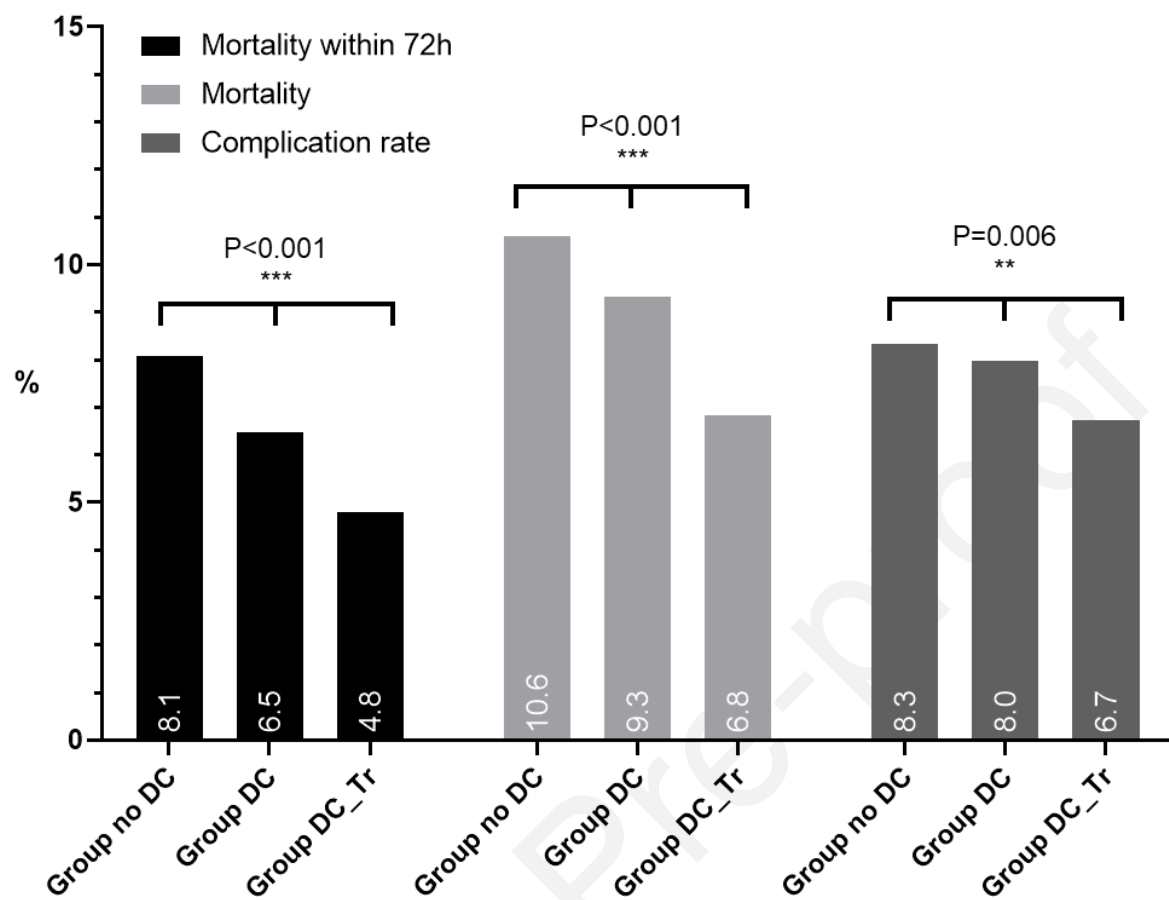
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LEGENDS

FIGURE 1 Results regarding complications between 3 groups: DC; No DC and DC Tr

DC: Damage control; **No DC:** No Damage control; **DC Tr:** Damage control and application of new transfusion guidelines

TABLE 1 Changes in resuscitation strategies

| Author | Year | Patient Number | Origin | Main finding |
|----------|------|----------------|----------------|--|
| Gonzalez | 2007 | 200 | Level 1 Center | FFP should be administered during resuscitation, not just volume |
| Duchesne | 2010 | 124 | Level 1 Center | DCR and DCL improve survival and reduce ICU stay |
| Cotton | 2011 | 390 | Level 1 Center | Damage Control Resuscitation improves 30 days survival |
| Holcomb | 2015 | 680 | PROPPR Study | 1:1:1 plasma:platelet:pRBCs improves 24 hours exsanguination |
| Perl | 2016 | 346 | PROPPR Study | No side effect by permissive resuscitation on emergency laparotomy |
| Meyer | 680 | 680 | PROPPR Study | Critical administration threshold should be respected |
| Robinson | 454 | 454 | PROPPR Study | Excess crystalloids increase the risk of ARDS |

FFP = Fresh Frozen Plasma

DCR = Damage Control Resuscitation

DCL = Damage Control Laparotomy

pRBCs = packed Red Blood Cells

ARD = Acute Respiratory Distress Syndrome

TABLE 2 Summary of coagulation tests recommended in guidelines, multi center studies and systematic reviews. Also, threshold levels for dynamic platelet function tests regarding prediction of various complications are listed, along with comparative parameters indicated in the studies

| Author | year | Patients | Endpoint Parameter | Comparative parameter |
|---------------------------------------|------|-------------------|----------------------|-----------------------|
| <i>Guidelines/Reviews</i> | | | | |
| Rugieri | 2007 | General trauma | INTEM CA15 | Platelet count |
| Holcomb | 2012 | ER patients | r-TEG (non-specific) | CCTs |
| Veigas | 2016 | Systematic review | EXTEM/INTEM | multiple CCTs |
| Spahn | 2019 | Guideline | all | multiple CCTs |
| Schochl | 2019 | Multicenter | all | multiple CCTs |
| <i>Prediction of Mortality</i> | | | | |
| Levrat | 2008 | General trauma | EXTEM MCF/APTEM | ELT<90min |
| Schochl | 2009 | General trauma | FIBTEM MCF/EXTEM | none |
| Tauber | 2011 | see above | FIBTEM/EXTEM | CCT |
| Rourke | 2012 | General trauma | EXTEM/FIBTEM | none |
| <i>Prediction of mass transfusion</i> | | | | |
| Leemann | 2010 | General trauma | EXTEM/INTEM | CCT |
| Tauber | 2011 | Polytrauma | FIBTEM MCF | CCT |
| Schochl | 2011 | Head injury | FIBTEM | CCT |
| Davenport | 2011 | General trauma | EXTEM | CCT |
| <i>All transfusions</i> | | | | |
| Hagemo | 2015 | General trauma | EXTEM/FIBTEM | CCT |
| Schochl | 2010 | Major Trauma | EXTEM/FIBTEM | CCT |

CCT = Conventional Coagulatory tests

ELT = Euglobulin Lysis Time

TABLE 3 Recommended lactate threshold levels and availability of lactate clearance data – all trauma patients

| Author | Year | Lactate Threshold (admission) | Lactate Clearance (24 hours) | Other comparative values | |
|------------|------|-------------------------------|------------------------------|--------------------------|-------------------|
| Husain | 2003 | 2.0 mmol/l | arterial | 2.0 mmol/l | BD, Apache II |
| Pape | 2005 | 2.5 mmol/l | n.a. | n.a. | > 6 |
| Billeter | 2009 | 2.5 mmol/l | arterial | 2.5mmol/l | PCT, II-6 |
| Regnier | 2012 | 2.0 mmol/l | n.a. | 2.2mmol/l at 2,4 hours | RTS, TRISS |
| Odom | 2013 | 2.5 mg/dl | n.a. | 2.5 mmol/l at 6 hours | n.a. |
| Vallier | 2014 | 4.0 mmol/l | n.a. | n.a. | pH 7.25 |
| Dezman | 2015 | 3.0 mmol/l | venous | 2.0 mmol/l | Age, ISS, adm. BP |
| Contenti | 2015 | 2.2 mmol/l | mismatch | n.a. | none |
| Dekker | 2017 | 2.5 mmol/l | no difference | 2.5 mmol/l | ISS, TRISS |
| Dezman | 2018 | 3.0 mmol/l | venous | 2.0 mmol/l | n.a. |
| Thienhoven | 2019 | 2.0 mmol/l | arterial | n.a. | n.a. |

BD = Base Deficit

n.a. = not available

PCT = Procalcitonine

IL = Interleukine

RTS = revised Trauma Score

TRISS = Trauma Injury Severity Score

ISS = Injury Severity Score

Adm. = admission

BP = Blood Pressure

TABLE 4 Comparison of parameters to perform various scores performed for grading of polytrauma patients in the orthopaedic literature

| Categories | | Score | | | |
|--------------------------|------------------------------------|------------|------|-------------|-------------|
| | | CGS | EAC | mCGS | PTGS |
| | | 2005 | 2013 | 2014 | 2014 |
| Shock | | | | | |
| | SBP, mmHg | x | | x | x |
| | PBRC | (2 hrs) | | (24 hrs) | (48 hrs) |
| | Lactate, mmol/L | x | x | x | |
| | BE, mEq/L | x | x | x | x |
| | pH | | x | | |
| | ATLS score | x | | | |
| | Urine output | x | | | |
| Coagulopathy | | | | | |
| | Platelet count | x | | x | |
| | Factor II/V | x | | | |
| | Fibrinogen | x | | | |
| | D-Dimer | x | | | |
| | INR < 2 | | | | x |
| Admission Temperature | | x | | x | |
| Soft Tissue Injury | | | | | |
| | PaO ₂ /FiO ₂ | x | | | |
| | AIS chest | x | | x | |
| | Thoracic Trauma Score | x | | | |
| | Moore OIS | x | | x | |
| | Extremity AIS | x | | x | |
| | Pelvic trauma AO | x | | | |
| Injury Severity | | | | | |
| | NISS | | | | x |

(m)CGS = (modified) Clinical Grading Score

EAC = Early Appropriate Care

PTGS = PolyTrauma Grading Score

SBP = Systolic Blood Pressure

PBRC = Packed Red Blood Cells

BE = Base Excess

ATLS = Advanced Trauma Life Support

INR = International Normalized Ratio

AIS = Abbreviated Injury Scale

OIS = Organ Injury Score

AO = Arbeitsgemeinschaft für Osteosynthesefragen

NISS = New Injury Severity Score

Journal Pre-proof

TABLE 5 Injury severity level in clinical studies and comparison of indications for early definitive techniques and damage control orthopedics

| Author | Year | Setting | DC use | Mean ISS surgery <24h Early definitive surgery | Mean ISS surgery >24h Damage control | Conclusion |
|------------|------|------------------|--------------------------------|---|---|---|
| Nowotarsky | 2000 | single center | n.a. (112/1507, all femurs) | n.a. | n.a. | DC is safe in selected patients |
| Brundage | 2002 | single center | n.a. 157/674 nonoperative | - | - | Early operation is beneficial |
| Taeger | 2005 | single center | 30.70% | 30.4 | 37.3 | TRISS 20 vs 39% 29.5 vs 24.3% TRISS |
| Pape | 2007 | 10 centers (RCT) | n.a. | 23.3 | 29 | Early fixation in stable, DCO in unstable |
| Morshed | 2009 | Registry (NTDB) | n.a. | 27.2 | 32.3 | Less mortality in DCO with abd. trauma |
| Tuttle | 2009 | single center | 8.40% | n.a. | n.a. | DCO is safe |
| O'Toole | 2009 | single center | n.a. | 27.4 | 36.2 | DCO rarer than in Europe |
| Lefaiivre | 2010 | 2 centers | 21.4% and 2.77% | n.a. | n.a. | No difference |
| Nahm | 2011 | single center | n.a. | 28.8 | 36.4 | Early definitive care |

| | | | | | | |
|-------------|------|-------------------|-------|---------------------|------|---------------------------------------|
| Vallier | 2013 | single center | n.a. | exFix in late group | n.a. | Early definitive care |
| Steinhausen | 2014 | Registry (TR-DGU) | n.a. | 23.5 | 31.1 | “Risk –adapted “, if in doubt: DCO |
| Pape | 2019 | single center | 27.1% | 26.5 | 30.3 | risk adapted DCO in unstable patients |

DC = Damage Control

TRISS = Trauma Injury Severity Score

DCO = Damage Control Orthopaedic

n.a. = Not available

RCT = Randomized Controlled Trial

NTDB = National Trauma Data Base

TR-DGU = Trauma Register Deutsche Gesellschaft für Unfallchirurgie (German Society for Trauma Surgery)

h = hours

TABLE 6 Demographics of included patients from a database (level 1 trauma center)

| | |
|---|---------------------|
| n | 3668 |
| Age, mean (SD) | 45.8 (20.1) |
| Sex, male n (%) | 2694 (73.4) |
| Mortality within 72h, n (%) | 709 (19.4) |
| Emergency Surgery at admission, n (%) | 2592 (74.4) |
| Duration of emergency surgery, mean (SD) | 111.4 (96.6) |
| Length of Stay, mean (SD) | 16.9 (18.7) |
| ICU Stay, mean (SD) | 8.2 (10.5) |
| Duration Ventilation, mean (SD) | 5.1 (8.1) |
| AIS Head, mean (SD) | 2.8 (1.9) |
| AIS Face, mean (SD) | 0.6 (1.0) |
| AIS Thoracic, mean (SD) | 1.6 (1.7) |
| AIS abdomen, mean (SD) | 1.0 (1.7) |
| AIS spine, mean (SD) | 0.8 (1.4) |
| AIS pelvis, mean (SD) | 0.6 (1.2) |
| AIS extremity, mean (SD) | 1.3 (1.4) |
| ISS, mean (SD) | 28.2 (15.1) |

| | |
|--|--------------------|
| NISS, mean (SD) | 37.1 (17.4) |
| GCS admission, mean (SD) | 8.8 (5.5) |
| Lactate admission, mean (SD) | 2.9 (2.5) |
| Hemoglobin admission, mean (SD) | 11.4 (4.0) |
| ROTEM Intem CT admittion, n (%) | 193 (5.3) |
| Mortality, n (%) | 982 (26.8) |
| Pneumonia, n (%) | 623 (19.1) |
| Sepsis, n (%) | 546 (15.0) |
| Septic shock, n(%) | 119 (3.3) |
| Bacteremia, n(%) | 254 (7.9) |

n = Number

SD = Standard Deviation

h = Hours

ICU = Intensive Care Unit

AIS = Abbreviated Injury Scale

(N)ISS = (New) Injury Severity Score

GCS = Glasgow Coma Scale

TABLE 7 Variability of lactate threshold levels and recommendations of surgical timing in the orthopaedic literature.

| Author | Journal | year | Patient Number | Inclusion period | Time of surgery | Lactate threshold |
|-------------------|--|------|----------------|------------------|-----------------|-------------------|
| O'Toole Probst | J. Trauma-Injury Infect. Crit. Care | 2009 | 582 | 2002-2005 | 24 hours | 2.5mmol/l |
| Vallier | J. Orthop. Trauma | 2013 | 1443 | 1999-2006 | 24 hours | 4 mmol/l |
| Nahm | J. Trauma Acute Care Surg | 2014 | 1443 | n.a. | 24 hours | 4 mmol/l |
| Vallier | J. Orthop. Surg. Res | 2015 | 335 | 30 months | 36 hours | 4 mmol/l |
| Weinberg | J. Orthop. Surg. Res | 2015 | 332 | 2010-2013 | 36 hours | 4 mmol/l |
| Vallier | J. Orthop. Trauma | 2016 | 253 | 18 months | 36 hours | n.a. |
| Childs | J. Orthop. Trauma | 2017 | 376 | 30 months | 24 hours | 2 mmol/l |

TABLE 8 Comparison of published treatment guidelines and protocols

| | ETC | DC | <i>EAC</i> | <i>SDS</i> | <i>PRISM</i> |
|---|--------------------------|--------------------------|-------------------|-------------------|---------------------|
| Year of Introduction | 1989 | 2000 | 2013 | 2015 | 2016 |
| Supportive Prosp. Randomized study | Yes (Ref 165) 1989 | Yes (Ref 12) 2007 | No | No | No |
| Supportive Registry analysis | No | Yes (Ref 163) 2014 | No | No | No |
| Matched pair analysis | No | Yes (Ref 162) 2011 | No | No | No |

Table 9 Parameters to assess the patient at risk, comparison between 2000 and currently.

Parameters to assess the borderline trauma patient - comparison between 2000 and now

| | | 2000 | 2020 <i>unchanged parameters</i> new parameters |
|--------------------------|---------------------------|--|---|
| Static parameters | <i>Injury combination</i> | <i>Polytrauma ISS > 20 and additional thoracic trauma (AIS >2)</i> | <i>Polytrauma ISS > 20 and AIS chest > 2</i> Thoracic Trauma Score (TTS) > grade 2 (> 3 rib fx, paO₂/FiO₂ <200, LuCo > 1 lobe, bilat.HT/HPT > unilat)) |
| | <i>Local injury chest</i> | <i>Bilateral lung contusion: 1st plain film</i> | <i>Bilateral lung contusion: 1st plain film or</i> Chest CT: <ul style="list-style-type: none"> • unilateral bisegmental contusion • bilateral uni- or bisegmental contusion • flail chest |
| | | | |

| | | | |
|----------------|--|--|--|
| | <i>Local injury trunk/extremities</i> | <i>Multiple long bone fractures + truncal injury AIS 2 or more</i> | <i>Multiple long bone fractures + truncal injury AIS 2 or more</i> |
| | <i>Truncal /</i> | <i>Polytrauma with abdominal /pelvic trauma RR ,90 mm Hg) (Moore 3) and hem. shock</i> | <i>Polytrauma with abdominal/pelvic trauma RR ,90 mm Hg) (Moore 3) and hemorrhagic shock</i> |
| | <i>Major Surgery for non-life saving conditions</i> | <i>Day 1 surgery (Early total care) or wait until 4-6 (window of opportunity)</i> | Non life saving surgeries Flexible (day 1, 2, 3) after reassessment according to individual patient physiology: Safe definitive surgery (SDS) and damage control (DCO) |
| | <i>Duration of 1st operative intervention</i> | <i>Presumed operation time > 6 hours</i> | <i>Presumed operation time > 6 hours</i> intraoperative reassessment: <ul style="list-style-type: none"> • coagulopathy (ROTEM/FIBTEM) • lactate (< 2.0 - 2.5 mmol/L) • body temperature stable • requirement > 3 pRBC / hour |
| Dynamic | | <i>Massive transfusion (10 units RBCs per 24 hours)</i> | |

| | | | |
|-------------------|---------------------------------------|---|---|
| parameters | <i>Blood transfusion requirements</i> | | <i>Massive transfusion</i> (10 units RBCs per 6 hours) initiates „goal directed therapy“ (massive transfusion protocols) |
| | <i>Intra/perioperative</i> | <i>PA-pressure increase during intramedullary nailing .6 mm Hg</i> <i>Initial mean PAP < 24 mm Hg</i> | <ul style="list-style-type: none"> • ROTEM/FIBTEM • Lactate clearance < 2.5 mmol/l (24 hrs.) |

LuCo = Lung contusion